II. Interview Summary

The Applicants' representative thanks the Examiner for telephone interview on October 21, 2008 during which the priority issue in connection with the above identified patent application was discussed. As stated in paragraph 6 at page 3 of the Office Action, Applicants are requested to provide evidence showing that US Application 07/971,857 was filed as a national stage application of PCT/GB91/01134. It was agreed during the telephone interview that Applicants would submit a request for corrected filing receipt and evidence showing that 07/971,857 was accepted as a national stage application.

III. Priority Claim

Applicants are submitting with this response a request for corrected filing receipt and a filing receipt copy of US Application 07/971,857 (one of the applications from which the present application claims its priority, Exhibit A) showing that the USPTO determined that PCT/GB91/01134 has met the requirements of 35 U.S.C. §371 and accepted US Application 07/971,857 for national patentability examination. Applicants further submit the front page of US Patent 5,969,108 (Exhibit B) that issued from US Application 07/971,857 showing that its 35 U.S.C. §371 date is January 8, 1993 and based on PCT/GB91/01134. This establishes that US Application 07/971,857 was a national stage application of PCT/GB91/01134, and thus that the priority claim for the above-identified patent application may be properly corrected.

IV. Preliminary Remarks

Paragraph 7 of the Office Action describes the invention as claimed. Page 4 states that "an antibody heavy chain variable domain includes the following structures: FW1-CDR1-FW2-CDR2-FW3-CDR3- FW4; CDR1; CDR2; CDR3; etc (i.e. any structure comprising an antibody variable domain)." However, CDR1; CDR2; or CDR3 is not a heavy chain variable domain.

The term of art is reserved for structure "FW1-CDR1-FW2-CDR2-FW3-CDR3- FW4" which is made up of three complementarity determining regions (CDR1 and CDR2 and CDR3) separated by four framework regions (FR1, FW2, FW3 and FW4). See paragraph [0005] of the specification which supports this explanation.

> [0005] . . . The heavy chains have four domains, one corresponding to the V region and three domains (1, 2 and 3) in the C region . . . each V region is made up from three complementarity determining regions (CDR) separated by four framework regions (FR).

See also *Taub* cited by the Examiner (page 259, right column, 2nd paragraph). See below.

V. Patentability Arguments

1. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

A. Rejection Over *Dower* in view of *Taub*

Page 5 of the Office Action states that claims 9 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Dower* et al. U.S. Patent 5,427,908 filed May 1, 1990 and *Taub* et al. JBC 264(1): 259-265, 1989.

It is further stated at page 5 that "*Dower* et al. teach methods of producing filamentous bacteriophage surface expressing binding domains of antibody fragments including VH that are encoded by nucleic acid sequences and screening the libraries of filamentous bacteriophage including fd, fl, and M13 expressing the VH and/or VL against various antigens, antigenic determinants, or haptens in order to select a specific binding domain." Emphasis added.

It is further stated at page 6 of the Office Action that the main focus of *Dower* et al. is screening for VH and VL combinations. Emphasis added.

It is then stated that *Taub* teach screening for binding of heavy chain CDR domains particularly CDR3 including competitive binding assays. The Office Action then concludes that claims 9 and 14-17 would be obvious over the *Dower/Taub* combination because the substitution

of one known element (phage-displayed VH-VL as taught by *Dower* et al.) for another (i.e. CDR alone as taught by *Taub* et al.) would have yielded predictable results (i.e. binding to epitopes/antigens) to one of ordinary skill in the art at the time of the invention. In addition, the claims would have been obvious because a particular known technique (i.e. phage display of polypeptides for screening assays as taught by *Dower* et al.) was recognized as part of the ordinary capabilities of one skilled in the art.

Applicants respectfully disagree with this conclusion because the structures in the cited art referred to by the Examiner differ from those presently claimed. In first, as discussed *supra* in this response, a CDR and a variable domain are two different structures. The term of art "variable domain" is reserved for structure "FW1-CDR1-FW2-CDR2-FW3-CDR3- FW4" which is made up from three complementarity determining regions (CDR1, CDR2 and CDR3). The Examiner cites *Taub* for disclosing a CDR alone.

Dower discloses:

> When the protein of interest is an antibody of a desired binding specificity, the antibody may be of any of the known isotypes or subclasses for a particular species, and may be a single-chain or two-chain binding complex or portion thereof. For instance, only the variable antigen-binding regions of heavy (V_H) and/or light (V_L) chains ***may be identified and cloned; the binding fragments (F_v) or Fab encoded thereby may find use either as a binding fragment, joined to constant regions of heavy or light chains, or joined to other proteins having desired effector functions.*** The characteristics of the constant region domains will depend to a large extent on the use intended for the antibody, e.g., diagnostic and/or therapeutic applications, catalytic antibodies, etc.

(Emphasis added.)

This passage does not state that the binding domain consists of an "...antibody heavy chain variable domain..." as required by the pending claims. The passage provides that ...V_H and/or V_L chains may be identified and cloned. It then states that,

> *...the binding fragments (F_V) or Fab encoded thereby may find use either as a binding fragment, joined to constant regions of heavy or light chains, or joined to other proteins having desired effector functions.*

F_V fragments consist of both a heavy chain variable region (V_H) and a light chain variable region (V_L) which together form an antigen binding site. *See* e.g. Figure 1 of the present application attached hereto as Exhibit A. Fab fragments consist of a V_L and a V_H, each of which (unlike the heavy chain variable domains of the present invention) comprise a constant region which when combined constitute an antigen binding fragment. *Id.* The passage in *Dower* referred to by the Examiner does not state that a heavy chain variable domain is a binding molecule. It refers to the combination of V_H and V_L that gives rise to the F_V and/or Fab binding fragments.

The cloning of V_H and/or V_L domains and their combinations are further elaborated in *Dower*, column 4, lines 51-64 where the use of separate cloning vectors for antibody light and heavy chain sequences is suggested from which a combinatorial library is constructed to bring together V_H and V_L domain sequences in associated pairs to form binding domains. Thus, *Dower* discloses that its method is useful for identification and cloning of a new variable V_H domain and V_L domain **which can be used to form F_V or Fab antigen** binding fragments and does not disclose the display of a binding molecule consisting of a V_H domain on the surface of a filamentous phage.

This interpretation is further supported by the fact that the claims of *Dower* are directed to screening a DNA library for nucleotide sequences which encode,

> ...an antibody Fab fragment comprising first and second polypeptide chains, one chain comprising a light chain variable region and another chain comprising a heavy chain variable region... (See claim 1)

Further, Example 1 of *Dower* is similarly directed to display of Fab molecules, in which one polypeptide chain composed of V_H and C_H domains is presented as a fusion with bacteriophage gene III protein and displayed with an associated second polypeptide composed of V_L and C_L domains to provide a binding domain formed by the combination of V_H and V_L chains and their associated constant regions together.

In summary, *Dower* does not disclose the display of an antibody heavy chain variable domain as required by the present claims.

At page 6 of the Office Action, it is stated that "the claim is obvious because the substitution of one known element (phage-displayed VH-VL as taught by *Dower* et al.) for another (i.e. CDR alone as taught by *Taub* et al.) would have yielded predictable results." Thus, the Examiner has concluded that the pending claims are obvious over the *Dower/Taub* combination based on factual assumption that all elements of the pending claims were known to a person skilled in the relevant art after reading *Dower* and *Taub*. As discussed above, the CDR of *Taub* and an antibody heavy chain variable domain of the pending claims are two different elements.

Applicants respectfully bring to the Examiner's attention Section 2143 of MPEP, which provides:

> To reject a claim based on combining prior art elements according to known methods to yield predictable results, Office personnel must resolve the *Graham* factual inquiries. Then, Office personnel must articulate the following:
>
> (1) *a finding that the prior art included each element claimed*, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference; . . .

MPEP, Section 2143(A) (emphasis added).

As explained in detail above, the cited art fails both alone and in combination to disclose a binding domain which consists of an antibody heavy chain variable domain, as recited by the pending claims. Therefore, the subject matter of the pending claims is not obvious over the *Dower/Taub* combination, and the rejection of the pending claims under 35 U.S.C. §103(a) may be property withdrawn; and withdrawal is respectfully requested.

B. Rejection Over *Ladner* in view of *Weir*

Claims 9 and 14-17 stand rejected at page 6 of the Office Action under 35 U.S.C. §103(a) allegedly as being obvious over a combination of WO 90/02809 ("*Ladner*") and *Weir* et al. J. Biochem. 100: 69-72, 1966 ("*Weir*"). *Ladner* discloses scFv comprising VH and VL on the surface of a filamentous bacteriophage particle. See page 6 of the Office Action. The Examiner agrees that *Ladner* does not teach the expression of V_H. See ¶1 at page 7 of the Office Action.

Weir is characterized at page 7 of the Office Action as teaching antigen binding assays for VH alone in the abstract; Tables 1-2; page 70, right column).

The *Weir* Abstract provides that the antigen-binding capacity has been studied by incubating a labeled antigen with its corresponding antibody and subsequent electrophoresis of antibody-antigen mixtures. The *Weir* conclusion was that that the heavy chains retained about 20% of the antigen-binding activity, while the light chains retained less than 5% of the activity. See the Abstract. (Emphasis added).

Thus, the *Weir* disclosure is limited to antibody light chains and heavy chains. The term of art "heavy chain" denotes a structure different from the term of art "V_H". See for example, the instant specification, which provides:

> [0005] Structurally, the simplest antibody (IgG) comprises four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulphide bonds (see FIG. 1). . . **The heavy chains have four domains, one corresponding to the V region and three domains (1, 2 and 3) in the C region.**

> . . . In even more detail, each V region is made up from three complementarity determining regions (CDR) separated by four framework regions (FR).

Emphasis added.

Thus, *Ladner* does not teach expression of the V_H, and for the reasons provided above, *Weir* does not teach the expression of V_H alone either.

It is stated at page 7 of the Office Action, that "the claim would have been obvious because the substitution of one known element (phage-displayed VH-VL as taught by Ladner et al.") for another (i.e. VH alone) would have yielded predictable results (i.e. binding of epitopes/antigens) to one of ordinary skill in the art at the time of the invention. However, *Weir* does not teach expression of VH.

Applicants respectfully bring to the Examiner's attention that as discussed in detail above, Section 2143 of MPEP provides that to establish a prima facie case of obviousness, the Examiner must allege a finding that the prior art included each element claimed.

Applicants further submit that for the reasons explained above, there is no finding that the *Ladner/Weir* combination discloses the binding domain of the binding molecules which consists of an antibody heavy chain variable domain, as recited by the pending claims. Therefore, the rejection of the pending claims under 35 U.S.C. §103(a) over the *Ladner/Weir* combination may be property withdrawn; and withdrawal is respectfully requested.

VI. Conclusion

In view of the above arguments, Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at (312) 846-5622.

Respectfully submitted,

HOWREY LLP

By: Kate Berezutskaya

Kate G. Berezutskaya, Ph.D.
Registration No.: 53,984
Customer No.: 22930
Direct Telephone No.: (312) 846-5622

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HOWREY LLP
ATTN: Docketing Department
2941 Fairview Park Drive, Suite 200
Falls Church, VA 22042-9922
Telephone No.: (703) 663-3600
Facsimile No.: (703) 336-6950